PATENT
Case: OC01000KQ US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
RYBAK *ET AL.*	Examiner: A. HOLLERAN
For:	Group Art Unit: 1642
MELANOMA THERAPY	
Serial No.: 09/904,263	
Filed: July 12, 2001	

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF CRAIG TENDLER, M.D.

I, Dr. Craig Tendler, declare and state as follows:

1. I earned a B.A. degree in Biological Sciences from Cornell University in 1980 and an M.D. degree from Mount Sinai School of Medicine in 1984. I was a pediatric intern and resident at Mount Sinai Hospital (New York, NY) from 1984-1988. I was a fellow at the National Cancer Institute, NIH from 1988-1991 and at Mount Sinai Hospital from 1991-1992. I was an assistant professor of pediatrics and pediatric oncology at Mount Sinai School of Medicine from 1992-1995. I am certified in Pediatrics (1988), Advanced Cardiac Life Support (1988) and Pediatric Hematology/Oncology (1992). Attached is a copy of my *curriculum vitae* (Exhibit A).

2. Since 1995, I have been at Schering-Plough Corporation, the assignee of the present patent application. I am currently Vice President, Oncology Clinical Research and Chair, Oncology Licensing Committee. At Schering-Plough, I have supervised clinical trials using INTRON A (interferon alpha 2b) and PEG-INTRON (a pegylated interferon alpha 2b) to treat high-risk malignant melanoma for the past eight years. I supervised the pivotal trials leading to approval of INTRON A for melanoma treatment by the Food and Drug Administration and other national health authorities.

3. I am familiar with the January 29, 2003 and May 20, 2003 Office Actions issued in the above-identified application. With respect to claims 1, 3-7, 9, 11, 12 and 14-17, I am aware that the Examiner is of the opinion that

> it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted pegylated interferon alpha-2b for the unconjugated interferon alpha-2b of Kirkwood [Kirkwood et al., J. Clin. Oncol. 14(1): 7-17 (1996); hereafter Kirkwood], because of the art-recognized benefits of pegylation as taught by Gilbert [Gilbert et al., United States Patent 5,951,974, hereafter Gilbert] and Glue [Glue et al., United States Patent 5,908,621; hereafter Glue] and demonstrated by Talpaz [Talpaz et al., Blood 92(10): 251a (1998); hereafter Talpaz].
>
> See January 29, 2003 Office Action, page 4.

With respect to claims 1, 3-7, 10, 11, 13 and 14, I am aware that the Examiner is of the opinion that

> it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted pegylated interferon alpha-2a for the unconjugated interferon alpha-2b of Creagan [Creagan et al., J. Clin. Oncol. 13(11): 1776-1783 (1995); hereafter Creagan], because of the art-recognized benefits of pegylation as taught by [Gilbert] and [Glue].
>
> See January 29, 2003 Office Action, page 5.

4. I make this declaration to explain why the references cited by the Examiner were not predictive of the successful use of pegylated interferon alpha in the treatment of melanoma at the time the invention was made. I have reached this conclusion for the following reasons, which are discussed in detail in ¶¶ 5-11:

- Using unpegylated interferon alpha to treat melanoma was not predictive of using pegylated interferon alpha to safely and efficaciously treat the disease because pegylated and unpegylated interferon alpha are structurally and functionally distinct drugs;

- Successfully treating hepatitis C with pegylated interferon alpha was not predictive of effectively treating melanoma with pegylated interferon alpha because these diseases have dissimilar etiologies and effects; and

- Safely treating melanoma with pegylated interferon alpha could not be predicted by treating hepatitis C with the drug due to the likelihood that higher doses would have to be used for melanoma compared to those used for hepatitis C.

5. At the time the invention was made, it was known that the molecular and pharmacokinetic properties of pegylated interferon alpha and interferon alpha were substantially different from one another, such that the two molecules should be considered to be different drugs. Pegylation changes the chemical nature of the molecule from a protein to a protein-polymer conjugate and increases its molecular weight. For example, PEG-INTRON, a pegylated interferon alpha 2b, has a molecular weight of 31 kDal, compared to a molecular weight of approximately 19 kDal for unpegylated interferon alpha 2b. Pegylation of interferon alpha also decreases the specific activity of the drug by approximately 30% while increasing the plasma half-life by more than ten-fold compared to that of unconjugated interferon alpha.

6. It was also known when the invention was made that the increased half-life of pegylated interferon alpha relative to that of the unpegylated form significantly alters certain pharmacokinetic properties of the pegylated molecule. Specifically, the relationship of peak plasma levels to total drug exposure is different for pegylated interferon alpha compared to that of unpegylated interferon alpha.[1] For example, for the doses used in melanoma treatment, administration of pegylated interferon alpha as compared to unconjugated interferon alpha results in lower peak plasma levels of interferon alpha activity but prolongs total drug exposure as compared to administration of unconjugated interferon alpha.

7. At the time the invention was made, it was known that a particular pharmacokinetic parameter of a drug was often essential for treating a particular disease. It was known that, in some cases, a patient's total exposure to the drug (AUC) was critical for treatment. For instance, the total drug exposure to interferon alpha appears to be the most significant parameter in the treatment of chronic myelogenous leukemia using unpegylated interferon. It was also known that, in other cases, the peak plasma level of a drug (C_{max}) was important for successfully treating a disease. For example, it seems that the peak plasma level of unpegylated interferon alpha is critical for treating melanoma successfully. This demonstrates that the peak plasma level of a particular drug may be essential for treating one disease while the total drug exposure of the same drug may be important for treating a different disease. It was also known at the time the invention was made that the total drug exposure of one drug may be

[1] Peak plasma level of a drug, also referred to as C_{max}, is a measurement of the maximum drug concentration achieved in a patient after administration of a drug. Total dose exposure, also referred to as the area under the concentration-time curve or AUC, measures a patient's total xposure to a drug over a period of time.

important for effectively treating a particular disease, while the peak plasma lev l of a different drug may be critical for treating the same disease.

8. In my opinion, the efficacy of a drug with respect to a particular disease could not have been predicted at the time the invention was made based upon treatment of that disease with a structurally and functionally distinct drug. One could not have predicted for pegylated interferon alpha whether the total drug exposure or its peak plasma level was important for predicting anti-melanoma activity based upon the efficacy of unconjugated interferon alpha in treating melanoma because pegylated interferon alpha and unconjugated interferon alpha are different drugs with different pharmacokinetic profiles (see ¶¶ 5-7 above).

9. The efficacy of a drug with respect to a particular disease also could not have been predicted based upon treatment of a different disease with the same drug. The use of pegylated interferon alpha to treat hepatitis C was not predictive of its effectiveness in the treatment of melanoma because it was known that interferon alpha-mediated antiviral mechanisms may well be different than interferon alpha-mediated anti-melanoma mechanisms. Similarly, the use of pegylated interferon alpha to treat chronic myelogenous leukemia (CML) was not predictive of its effectiveness in treating melanoma because these diseases have dissimilar etiologies and effects.

10. It was also unpredictable at the time the invention was made whether pegylated interferon alpha would be safe in treating melanoma based upon treatment of the disease with unconjugated interferon alpha. As discussed above, administration of pegylated interferon alpha in the doses used for melanoma results in drug exposures that are more prolonged and thus higher than those achieved using unpegylated interferon alpha. See ¶ 6 above. It was unknown at the time the invention was made whether such high total drug exposure levels for the time periods necessary to successfully treat melanoma would lead to unacceptable side effects. Although the Examiner asserts that "pegylation of interferon alpha reduces side-effects and would allow the administration of higher doses of interferon alpha" (see the January 29, 2003 Office Action, page 4), this is not necessarily the case. It was recognized in the art that administering pegylated interferon alpha at high doses might cause side effects severe enough that treatment would have to be discontinued. "[T]he maximal dose for mammals including humans is the highest dose that does not cause unmanageable clinically-important side effects." Gilbert, col. 11, lines 22-25. Thus, although Kirkwood

and Creagan state that unconjugated interferon alpha can be successfully used to treat melanoma, one skilled in the art could not have predicted when the invention was made whether the pegylated form of interferon alpha would be both safe and efficacious in treating the disease.

11. Further, although treating hepatitis C or CML with pegylated interferon alpha was known to be safe, this was not predictive of the drug's safety in effectively treating melanoma at the time the invention was made. It was known that the standard dose of unpegylated interferon alpha for treating melanoma was higher than that for hepatitis C. For example, the standard dose of unpegylated interferon alpha for hepatitis C is 3 million international units (MIU) three times weekly (a total of 9 MIU/week). In contrast, the standard dose of unpegylated interferon alpha for melanoma is 20 MIU/m^2 five days a week (100 MIU/m^2/week) for four weeks followed by 10 MIU/m^2 three times weekly (30 MIU/m^2/week) for 48 weeks. See, e.g., Kirkwood, page 8, left column.[2] Thus, one skilled in the art would have expected that higher doses of pegylated interferon alpha might have to be administered to treat melanoma compared to the doses used for treating hepatitis C. Given that it was known that pegylated interferon alpha provided greater total drug exposure because of its longer half life and that high doses of pegylated interferon alpha might cause unmanageable side effects, one skilled in the art could not have predicted at the time the invention was made whether there was a dose that could be used to treat melanoma effectively and safely. With respect to CML, Schering-Plough conducted Phase I studies for both hematologic malignancies, such as CML, and solid tumors, such as melanoma, because of the concern that there may be different drug tolerability profiles for these two types of diseases. Thus, although it was known that pegylated interferon alpha was safe for treating hepatitis C and CML, as stated by Glue and Talpaz, one skilled in the art could not have predicted whether the pegylated form of interferon alpha would be safe for treating melanoma when the invention was made.

[2] The average body surface area is 1.8 m^2.

12. All statements made herein of my own knowledge are true and that all statements made on information and b lief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application and any patent issued thereon.

20 Oct. 2003
Date

Craig Tendler
Craig Tendler, M.D.

EXHIBIT A

CURRICULUM VITAE
Craig L. Tendler, M.D.

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EDUCATION:

Undergraduate: 1976-1980
B.A., Biological Sciences,
Cornell University

Graduate: 1980-1984
M.D.,
Mount Sinai School of Medicine

MAJOR ACCOMPLISHMENTS:

- CPMP submission of CAELYX for breast cancer – Feb. '02
- CPMP approval of CAELYX for ovarian cancer – Oct. '00
- FDA approval of INTRON for non-Hodgkin's lymphoma – Oct. '97
- FDA and CPMP approvals of INTRON for malignant melanoma – Jan. '96

HONORS AND AWARDS:

for

1991: Charles Revson Foundation Award
1990: Henry Christian Award - American Federation Clinical Research
1988: Pediatric Scientist Training Award
1988: Who's Who, Young American Professionals
1984: Bela Schick Pediatric Society Prize
1984: Alpha Omega Alpha Honor Medical Society

CURRENT LICENSURE/CERTIFICATION:

Licensure:

1991: New Jersey, #56755
1985: New York, #165111

Certificati n:

1992: Sub-Board Pediatric Hematology/Oncology
1988: Advanced Cardiac Life Support
1988: American Board of Pediatrics
1985: National Board of Medical Examiners

ACADEMIC/HOSPITAL APPOINTMENTS:

Assistant Professor of Pediatrics (Adjunct), Mount Sinai School of Medicine, 1995-99

COMMITTEES/SOCIETIES/PROFESSIONAL AFFILIATIONS:

1998: International Society of Interferon and Cytokine Research
1997: American Society of Clinical Oncology
1994: Pediatric Oncology Group
1994: American Society of Hematology
1991: Fellow of the American Academy of Pediatrics
1988: Associated Alumni of Mount Sinai

WORK EXPERIENCE:

Present:	Vice President, Oncology Clinical Research and Chair, Oncology Licensing Committee
2000-2001:	Senior Director, Clinical Research, Schering-Plough Research Institute
1999-2000:	Director, Clinical Research, Schering-Plough Research Institute
1997-99:	Senior Associate Director, Clinical Research, Schering-Plough Research Institute
1995-97:	Associate Director, Clinical Research, Schering-Plough Research Institute, Kenilworth, New Jersey
1992-95: of	Assistant Professor of Pediatrics and Pediatric Oncology, Mount Sinai School Medicine, New York, New York
1991-92:	Pediatric Hematology/Oncology Fellow, Mount Sinai Hospital, New York, New York
1988-91:	St. Jude Oncology Fellow of the Pediatric Scientist Training Program National Cancer Institute, NIH, Bethesda, Maryland
1987-88:	Pediatric Chief Resident, Mount Sinai Hospital, New York, New York
1984-87:	Pediatric Intern and Resident, Mount Sinai Hospital, New York, New York

RELEVANT TRAINING:

Course subject area taken	Title	Year
Training	SOP Review and Compliance Training	2001
Training	SOP Update Workshop	2000
Training	PROSIT Resource Allocation	2000
Project Management	Portfolio Analysis for Pharmaceutical Research	1999

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13. Solal-Celigny P, Lepage E, Brousse N, Tendler CL, Brice P, Haioun C, Gabarre J, Pignon B, Tertian G, Bouabdallah R, Rossi, JF, Doyen C, Coiffier B. Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: Final analysis of survival and toxicity in the GELF 86 trial. J Clin Oncol 1998;16:2332- 38.

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15. Srivastava DK, Tendler CL, Milani D, English MA, Licht JD, Wilson SH. The HIV-1 transactivator protein tat is a potent inducer of the human DNA repair enzyme β-polymerase. AIDS 2001;15:433-40.

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ABSTRACTS

1. Tendler CL, Greenberrg SJ, Blattner W, Manns A, Waldmann, TA. Variable expression of the HTLV-I regulatory transcript pX in the adult T-cell leukemia (ATL) and the tropical spastic paraparesis (TSP) may reflect different stages of retroviral infection. Blood. Abstract 1989;74 (Suppl):764.

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